IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Boris Tabakoff et al.	
Application No.	09/171,697	NOW U.S. Patent No. 6,962,930 B1
Filed:	October 23, 1998	Granted: Nov. 8, 2005
For:	COMPOUNDS, COMPOSITIONS AND METHOD SUITABLE FOR AMELIORATION OF WITHDRAWAL SYNDROMES AND WITHDRAWAL-INDUCED BRAIN DAMAGE	Attorney Docket No. TBK-102

REQUEST FOR CERTIFICATE OF CORRECTION

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

United States Letters Patent No. 6,962,930 B1 was granted to Boris Tabakoff, Lawrence Snell, and Paula L. Hoffmann on November 8, 2005, on the basis of the above application, and is assigned to Lohocla Research Corporation. A number of printing errors were made by the Patent and Trademark Office during printing as summarized on the enclosed Patent Office Form PTO/SB/44 (4 pp.).

With regard to the errors noted in Columns 5 and 8, please refer to the Preliminary Amendment dated June 14, 1999 (copy enclosed) in which substitute pages 8 and 11 were filed depicting the correct formula.

It is requested that a Certificate of Correction be issued embodying the enclosed corrections.

Respectfully submitted,

Date: May 15, 2006

By _____
Talivaldis Cepuritis (Reg. No. 20,818)

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,962,930 B1

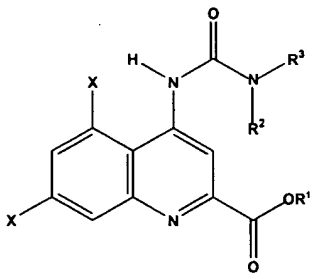
APPLICATION NO.: 09/171,697

ISSUE DATE : November 8, 2005

INVENTOR(S) : Boris Tabakoff et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5,
The formula appearing at lines 53-64 should be depicted as follows:



Column 6,
Line 11, "–NR^aR_b," should be -- –NR^aR^b, --.

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PATENT NO. : 6,962,930 B1

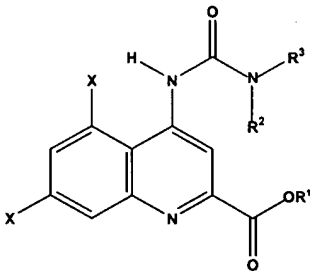
APPLICATION NO.: 09/171,697

ISSUE DATE : November 8, 2005

INVENTOR(S) : Boris Tabakoff et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8,
The formula appearing at lines 1-13 should be depicted as follows:



Column 9,
Line 2, after "R^{1}" delete the comma (,).

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PATENT NO. : 6,962,930 B1

APPLICATION NO.: 09/171,697

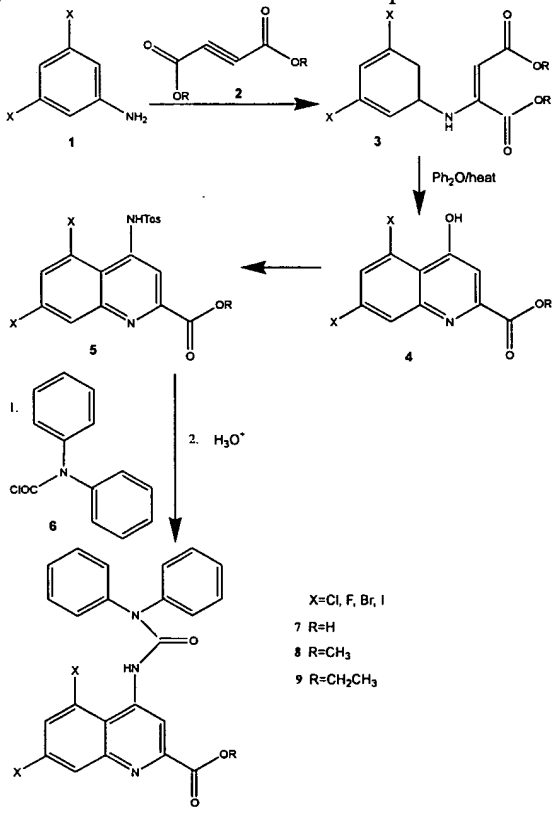
ISSUE DATE : November 8, 2005

INVENTOR(S) : Boris Tabakoff et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Columns 14-15,

The formulae bridging columns 14 and 15 should be depicted as follows:



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PATENT NO. : 6,962,930 B1

APPLICATION NO.: 09/171,697

ISSUE DATE : November 8, 2005

INVENTOR(S) : Boris Tabakoff et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 18,
Lines 34-50 should be deleted.

Column 25,
Line 39, "diameterxabout" should be -- diameter x about --.

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22 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Boris Tabakoff, et al.	
Serial No.	09/171,697	
National Filing Date:	October 23, 1998	Art Unit: Unknown
For:	Compounds, Compositions and Method Suitable for Amelioration of Withdrawal Syndromes and Withdrawal-Induced Brain Damage	
Examiner:	Unknown	Atty. Docket No. TBK-102-US

PRELIMINARY AMENDMENT

COPY

Assistant Commissioner for Patents
Washington, D. C. 20231

Sir:

Prior to examination, please amend the application as follows.

IN THE SPECIFICATION:

Substitute original page 8 with attached new page 8 submitted herewith.

Substitute original page 9 with attached new page 9 submitted herewith.

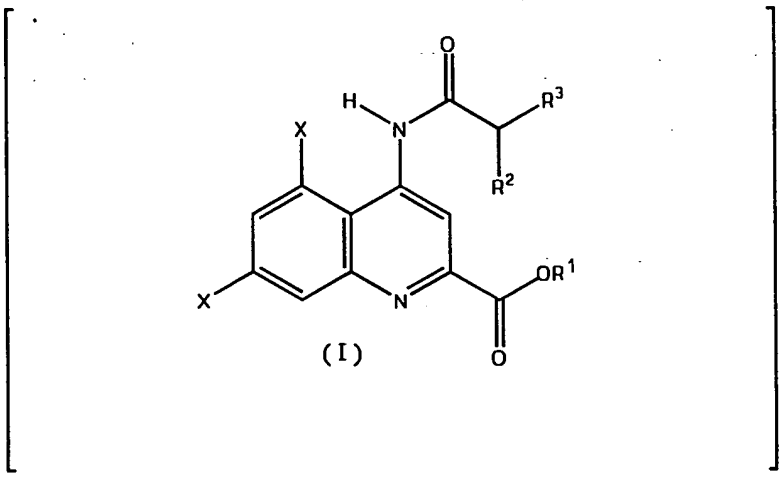
Substitute original page 11 with attached new page 11 submitted herewith.

Substitute original page 12 with attached new page 12 submitted herewith.

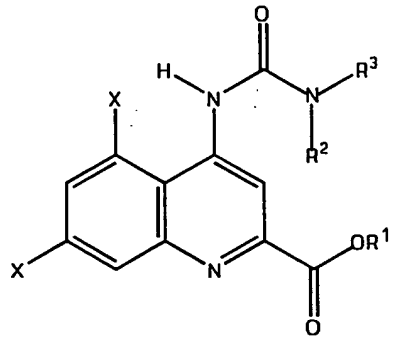
IN THE CLAIMS:

Rewrite Claim 1 as follows:

1. (Once-amended) A method suitable for treating withdrawal syndromes manifested in a patient suffering withdrawal symptoms and/or withdrawal-induced brain damage which comprises administering an effective ameliorating amount of a compound having the general formula (I):



(I)



(I)

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a tautomer thereof, a pharmacologically acceptable ester, amide, salt, ether, or an acid addition salt thereof;

wherein R^1 represents hydrogen or an alkyl group of 1 to 6 carbon atoms;

R^2 and R^3 each independently represent phenyl which may be unsubstituted or substituted one or more times with substituents selected from the group consisting of alkoxy, cycloalkoxy, alkyl, and cycloalkyl groups containing up to 6 carbon atoms, hydrogen, hydrocarbon selected from the group consisting of straight chain, branched, cyclic, and heterocyclic groups containing up to 18 carbon atoms, halogen, cyano,

trifluoromethyl, nitro, -OR^a, -SR^a, -NR^aR^b, [NR^aCOR^b] -NR^aCOR^b, -$NR^aCO_2R^b$, -$NR^aSO_2R^b$, -$NR^iCZNR^aR^b$, -CO_2, or -$CONR^aR^b$;

wherein R^a, R^b, R^i each independently represent hydrogen or hydrocarbon as described above and can be the same or different and Z represents oxygen, sulphur, or a group of formula =N,E; wherein E represents hydrocarbon as described above or an electron-withdrawing group; or

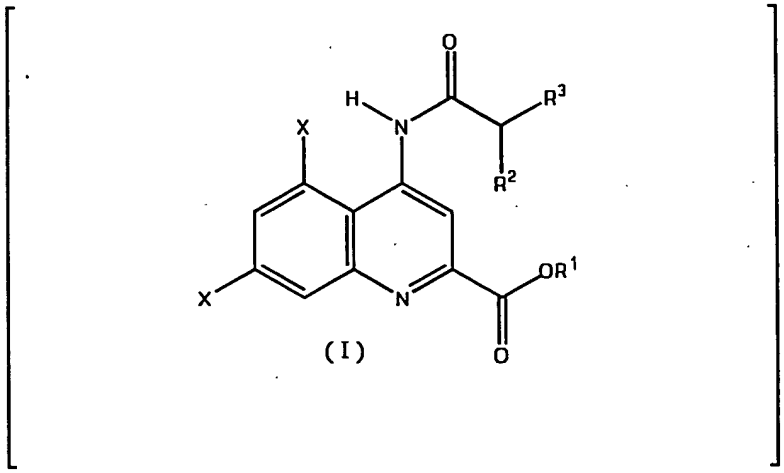
R^2 and R^3 together with the intervening nitrogen and carbon atom represent carbonyl (C=O), thiocarbonyl (C=S), imino (C=N,R^a), oximino (C=N,OR^a), or a 3- to 8-membered ring containing from zero to 4 hetero-atoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; wherein R^a represents hydrogen or hydrocarbon as described above;

wherein each of the R^2 and R^3 substituents can be the same or different; and

X represents halogen and each of the 5, 7, substituents can be the same or different.

Rewrite Claim 12 as follows:

12. (Once-amended) A compound suitable for treating withdrawal syndromes manifested in a patient suffering withdrawal symptoms and/or withdrawal-induced brain damage which comprises administering an effective ameliorating amount of a compound having the general formula (I):



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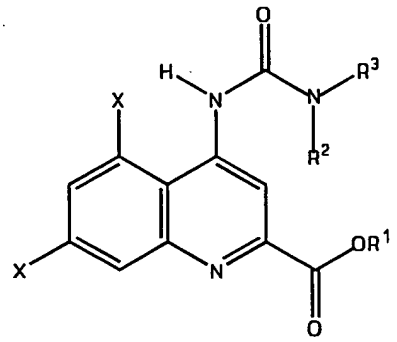

(I)

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a tautomer thereof, a pharmacologically acceptable ester, amide, salt, ether, or an acid addition salt thereof;

wherein R^1 represents hydrogen or an alkyl group of 1 to 6 carbon atoms;

R^2 and R^3 each independently represent phenyl which may be unsubstituted or substituted one or more times with substituents selected from the group consisting of alkoxy, cycloalkoxy, alkyl, and cycloalkyl groups containing up to 6 carbon atoms, hydrogen, hydrocarbon selected from the group consisting of straight chain, branched, cyclic, and heterocyclic groups containing up to 18 carbon atoms, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-NR^aR^b$, [NR^aCOR^b] $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-NR^aSO_2R^b$, $-NR^iCZNR^aR^b$, $-CO_2$, or $-CONR^aR^b$;

wherein R^a, R^b, R^i each independently represent hydrogen or hydrocarbon as described above and can be the same or different and Z represents oxygen, sulphur, or a group of formula =N,E; wherein E represents hydrocarbon as described above or an electron-withdrawing group; or

R^2 and R^3 together with the intervening nitrogen and carbon atom represent carbonyl (C=O), thiocarbonyl (C=S), imino (C=N,R^a), oximino (C=N,OR^a), or a 3- to 8-membered ring containing from zero to 4 hetero-atoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; wherein R^a represents hydrogen or hydrocarbon as described above;

wherein each of the R^2 and R^3 substituents can be the same or different; and

X represents halogen and each of the 5, 7, substituents can be the same or different.

For the Examiner's convenience, substitute pages 42 and 43 reflecting the amendments to claim 1 and substitute pages 44 and 45 reflecting the amendments to claim 12 are also attached.

REMARKS

During the international preliminary examination of the International PCT/US98/11312 application, from which the present national application stems, defects were noted in the structural formula of general formula (I) and in the description of the substituent groups which are being corrected by this Preliminary Amendment to the specification and claims.

The foregoing amendments, therefore, correct obvious and inadvertent typographical mistakes and conform the text with the claims for record clarification. No new matter is introduced. These same record clarifying corrections have been filed in the International PCT/US98/11312 application.

On substitute page 8, the nitrogen atom to which the R^2 and R^3 groups are attached in the structural formula (I) has been clarified and on line 21 the inadvertently omitted covalent bond symbol for the first listed substitutent group has been added. Support for the change to the structural formula (I) is provided by the description of the N-substituted compounds and the description of the synthesis on page 18. On substitute page 9, line 3, the identification of the substituent R groups has been clarified. On substitute page 11, the foregoing clarification to the structured formula (I) has been made. On page 12, lines 9 and 14, the same foregoing record clarifying corrections to the substituent groups have been made.

Early and favorable consideration of this application is respectfully solicited.

Respectfully submitted,

By _____
Dolores T. Kenney (Reg. No. 31,269)

June 14, 1999

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Serial No. 09/171,697 - - - - - 6
Atty. Docket No.: TBK-102-US

June 14, 1999

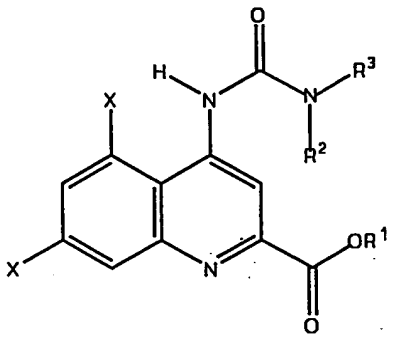
CERTIFICATE OF MAILING

I hereby certify that this Preliminary Amendment is being deposited with the United States Postal Service postage prepaid as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on June 14, 1999.

Mariejose Gordon

withdrawal or withdrawal-induced brain damage manifested in a patient suffering withdrawal symptoms is disclosed. The term "withdrawal syndromes" as used herein includes, but is not limited to, manifestations of one or more symptoms of CNS hyperexcitability associated with alcohol withdrawal syndromes, neuroexcitability disorders associated with drug withdrawal syndromes, neural brain damage induced by alcohol or drug dependence withdrawal and like neurodegenerative disorders associated with chronic drug use and withdrawal.

A preferred method comprises administering a physiologically effective amount of a compound having the general formula (I):



(I)

a tautomer thereof, a pharmacologically acceptable ester, amide, salt, ether, or an acid addition salt thereof;

wherein R^1 represents hydrogen or an alkyl group of 1 to 6 carbon atoms;

R^2 and R^3 each independently represent phenyl which may be unsubstituted or substituted one or more times with substituents selected from the group consisting of alkoxy, cycloalkoxy, alkyl, and cycloalkyl groups containing up to 6 carbon atoms, hydrogen, hydrocarbon selected from the group consisting of straight chain, branched, cyclic, and heterocyclic groups containing up to 18 carbon atoms, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-NR^aSO_2R^b$, $-NR^iCZNR^aR^b$, $-CO_2$, or $-CONR^aR^b$; wherein R^a, R^b, R^i each independently represent hydrogen or hydrocarbon as described above and can be the same or different and Z represents oxygen,

sulphur, or a group of formula =N,E; wherein E represents hydrocarbon as described above or an electron-withdrawing group; or

R^2 and R^3 together with the intervening nitrogen and carbon atom represent carbonyl (C=O), thiocarbonyl (C=S), imino (C=N,R^a), oximino (C=N,OR^a), or a 3- to 8-membered ring containing from zero to 4 hetero-atoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; wherein R^a represents hydrogen or hydrocarbon as described above;

wherein each of the R^2 and R^3 substituents can be the same or different; and

X represents halogen and each of the 5, 7, substituents can be the same or different.

Administration of the compound can be by oral, intravenous, subcutaneous, intramuscular, intraperitoneal, transdermal or buccal means for therapeutic treatment.

Preferred compounds of the general formula (I) are N-substituted 4-ureido-5,7-dihalo-2-carboxy quinoline compounds. Particularly preferred compounds were derivatives of kynurenic acid, hereafter referred to generally as DCUK compounds. Presently preferred DCUK compounds are (N,N-diphenyl)-4-ureido-5,7-dichloro-2-carboxy-quinoline (DCUKA); (N,N-diphenyl)-4-ureido-5,7-dichloro-2-carboxy-quinoline methyl ester)(DCUK-OMe); and N-phenyl, N-[2-methoxy]phenyl)-4-ureido-5,7-dichloro-2-carboxy-quinoline (MeO-DCUKA) which demonstrate affinity for both the strychnine-insensitive glycine binding site on the NMDA receptor complex and voltage-sensitive sodium channels.

The inventive DCUK compounds beneficially possess activity in reducing drug withdrawal-induced and excitotoxin-induced CNS hyperexcitability and neuronal damage at doses devoid of CNS depressant effects. Even at high doses, the DCUK compounds efficiently inhibit, in a use dependent manner, voltage sensitive sodium channels and inhibit NMDA receptor function without inducing the adverse marked behavioral stimulation and ataxia effects associated with known NMDA receptor antagonists or voltage sensitive sodium channel blockers. Additionally, the inventive DCUK compounds beneficially reduce or prevent in vitro measures of glutamate excitotoxicity.

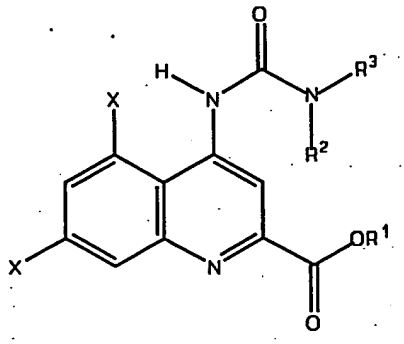
FIG. 13 shows the effects of (±)HA-966 on rotarod performance in naive C57BL/6 mice.

Detailed Description of Preferred Embodiment

Disclosed are compounds, compositions and a method suitable for treating dependence on, or preventing the withdrawal syndrome from being manifested during withdrawal from, the chronic use of ethanol, or other sedative or hypnotic or analgesic drugs in a patient (humans or other mammalian animal species). Withdrawal syndrome manifestations include, but are not limited to CNS hyperexcitability, such as tremors, insomnia, anorexia, disorientation, seizures, convulsions, anxiety or the like. The present compounds, compositions and method also provide for treating neurodegenerative disorders associated with chronic drug use and withdrawal induced brain damage.

The method provided by the present invention comprises administering by systemic means to a patient in need of such treatment or prevention an effective ameliorating amount of a compound which exhibits both an affinity for the strychnine-insensitive glycine binding site on the NMDA receptor complex and affinity for voltage-sensitive sodium channels (VSNaC).

A preferred compound embodiment has the general formula (I):



(I)

a tautomer thereof, a pharmacologically acceptable ester, amide, salt, ether, or an acid addition salt thereof;

wherein R^1 represents hydrogen or an alkyl group of 1 to 6 carbon atoms;

R^2 and R^3 each independently represent phenyl which may be unsubstituted or substituted one or more times with substituents selected from the group consisting of alkoxy, cycloalkoxy, alkyl, and cycloalkyl groups containing up to 6 carbon atoms, hydrogen, hydrocarbon selected from the group consisting of straight chain, branched, cyclic, and heterocyclic groups containing up to 18 carbon atoms, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-NR^aSO_2R^b$, $-NR^iCZNR^aR^b$, $-CO_2$, or $-CONR^aR^b$; wherein R^a, R^b, R^i each independently represent hydrogen or hydrocarbon as described above and can be the same or different and Z represents oxygen, sulphur, or a group of formula =N,E; wherein E represents hydrocarbon as described above or an electron-withdrawing group; or

R^2 and R^3 together with the intervening nitrogen and carbon atom represent carbonyl (C=O), thiocarbonyl (C=S), imino (C=N,R^a), oximino (C=N,OR^a), or a 3- to 8-membered ring containing from zero to 4 hetero-atoms selected from the group consisting of oxygen, nitrogen, sulphur and phosphorus; wherein R^a represents hydrogen or hydrocarbon as described above;

wherein each of the R^2 and R^3 substituents can be the same or different; and

X represents halogen and each of the 5, 7, substituents can be the same or different.

The term "alkyl" as used herein refers to lower alkyl groups containing less than 7 carbon atoms. A preferred alkyl group has 1 to 3 carbon atoms. The term "hydrocarbon" as used herein includes straight-chained, branched, and cyclic groups, including heterocyclic groups, containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. The term "halogen" as used herein includes chloro, fluoro, bromo and iodo substituents, preferably chloro. The term "alkoxy" as used herein refers to alkoxy groups containing less than 7 carbon atoms, preferably 1 to 3 carbon atoms. The term "substituted phenyl" refers to phenyl having one or more substituents selected from the group consisting of alkoxy, cycloalkoxy, alkyl, and